

## REMARKS

### **Pending Claims**

Claims 1-4, 11, 15, 19, 25, 26, 28, 29 and 37 are pending in the application.

Claims 11, 15, 19, 25, 26, 28, 29 and 37 are withdrawn from consideration

Claims 1-4 are rejected.

Claims 9, 10, and 16 are cancelled herein.

### **Claim Amendments**

Claim 1 has been amended to refer to "a core carbohydrate" rather than to "at least one core carbohydrate." In addition, claim 1 has been amended to include the limitations of cancelled claim 9.

Claim 19 has been amended to correct two typographical errors.

Claims 26 and 29 have been amended to more clearly describe the invention.

No new matter has been added.

### **Request for Rejoinder Reminder**

Applicants respectfully request rejoinder of method claims as set forth in Groups 23 and 24 upon allowance of the composition claims 1-4.<sup>1</sup> Towards that end, withdrawn method claims 25-26, 28 and 29 have been amended in a manner consistent with the pending composition claims.

Applicants again<sup>2</sup> request that the subject matter of claims 19 and 37 be included in the initial examination because clearly, if the product of claim 1 is patentable, then the addition of a peptide to the maleimide structure is also patentable.

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<sup>1</sup> Rejoinder was previously requested in the response to the July 10, 2007 Office Action.

Applicants additionally request that the subject matter of claim 15 be included in the initial examination because it is clear that if the product of claim 1 is patentable, then specification of the type of carbohydrate core as cyclodextrin is also patentable.

### **Rejection of Claims and Traversal Thereof**

In the September 27, 2007 Office Action:

claims 1-4, 9-10, and 16 were rejected under 35 U.S.C. §112, first paragraph; and

claims 1-4, 9-10, and 16 were rejected under 35 U.S.C. §103(a).

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

### **Rejection under 35 U.S.C. §112, first paragraph**

Claims 1-4, 9-10, and 16 were rejected under 35 U.S.C. §112, first paragraph because the Office contends that the specification “does not reasonably provide enablement for a maleimide cluster comprising more than one core carbohydrate” (page 3, No. 5 of the September 27, 2007 Office Action).

Amended claim 1 reads as follows:

**A maleimide cluster comprising a core carbohydrate molecule wherein the core is selected from the group consisting of monosaccharides, oligosaccharides, and cyclic oligosaccharides and wherein at least two or more maleimides are attached to the core and optionally comprising a protein covalently attached to the maleimide.**

According to page 3 of the Office Action, the specification is “enabling for a maleimide cluster comprising one core carbohydrate.” Thus, Applicants submit that claim 1, as amended herein, meets the

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<sup>2</sup> Inclusion of claims 19 and 37 in the initial examination was previously requested in the response to the July 10, 2007 Office Action.

requirements of 35 U.S.C. §112, first paragraph. Applicants therefore respectfully request that the rejection under 35 U.S.C. §112 be withdrawn.

### **Rejection under 35 U.S.C. §103(a)**

Claims 1-4, 9-10, and 16 were rejected under 35 U.S.C. §103(a) as being unpatentable over Brask et al. Journal of Peptide Science (2000), Vol. 6, pages 290-299 (hereinafter "Brask") and Nefzi et al. Tetrahedron Letters (1995), Vol. 36, pages 229-230 (hereinafter "Nefzi") in combination.

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

As noted above in amended claim 1, the present invention teaches a maleimide cluster comprising a core carbohydrate molecule wherein at least two or more maleimides are attached to the core and optionally comprising a protein attached to the maleimide.

Brask describes a process for creating synthetic proteins with a number of features critical to the function as desired and described therein. Specifically, Brask requires linkers (used to link a peptide to a template molecule) in its synthetic proteins in order to create moveable arms within the final structure. The linker arms are attached to peptides by means of an aldehyde group. Further, the carbopeptides formed by the Brask method are present in both cis and trans conformations, which is indicative of the dynamic structural nature of the final synthetic protein products of Brask (see Figures 4 and 5). Thus, it is clear that the synthetic proteins created by Brask contain moveable arms and are characterized as being present in both cis and trans conformational states in dynamic equilibrium. Clearly, flexibility is an important characteristic of the Brask molecules due to inclusions of moveable arms and different conformational states.

The movable and dynamic structure of Brask is in stark contrast to the rigid structure of the molecules described in Nefzi. Specifically, Nefzi describes a process for creating synthetic proteins, wherein a peptide is linked directly to a rigid template to create a predictable and stable structure. In the example supplied in Nefzi, the maleimide containing molecules are directly linked to a beta pleated sheet and the beta pleated sheet acts as a scaffold for four alpha helix proteins that are held erect and parallel, as shown in the illustration below.



$$T_4 - (4\alpha)$$

Importantly, the structure of Nefzi contains no linkers to create “moveable arms” or to allow any other types of conformational flexibility. Such linkers in Nefzi would serve to destroy the rigid structure that is necessary to support the four alpha helix proteins in the upright conformation as shown above.

It is incumbent upon the Office to clearly and explicitly state why the claimed invention would have been obvious in light of the cited references. According to the Federal Register, Vol. 72, No. 195, (Oct. 10, 2007), pp. 57528-57529, “Rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” In the Office Action of September 27, 2007, the Office simply offers brief descriptions of the templated synthetic proteins of Nefzi, which include a maleimide function, and the synthetic proteins of Brask, which are built on a carbohydrate core, and then closes the argument with the sentence “It would have been obvious to one of ordinary skill in the art at the time of the invention to attach peptides to a maleimide function covalently linked to a template.” (lines 14-15 of page 7 of the September 27, 2007 Office Action). The Office further states on page 7 that “[o]ne would have been motivated to incorporate a maleimide function because they are known to react rapidly and rather selectively with thiols. It would also have been obvious to one of ordinary skill in the art to select a monosaccharide as the template.” The Office’s statement is conclusory and overly simplistic, as it offers no reason why one of skill in the art would be motivated to combine the complex, specific and different chemical reactions of Nefzi and Brask. Therefore, the Office’s statement is legally insufficient by itself to establish *prima facie* obviousness.

The Office is still required to present a *prima facie* case of obviousness, even in light of the *KSR* decision, and which clearly has not been established by the proposed combination. Further, it is incumbent on the Office to view Applicants’ claimed invention as a whole. *In re Wesslau*, 174 U.S.P.Q. 393 (CCPA 1965). Concurrently, the Office must consider the inventions of any cited references in their respective entireties. Certain individual features from the references may not be arbitrarily chosen (while equally arbitrarily discarding other disclosed features) to merely lump together disparate features of different references as a mosaic in an attempt to meet the features of the rejected claims. Thus, the Office is not allowed to pick

and choose just certain parts of different references and combine them, **but instead, the references in their entirety must be considered.**

Applicants submit that if the teachings of Nefzi and Brask were combined, even though there is no suggestion for such combination, then the products of both Brask and Nefzi will be rendered unsatisfactory for its intended use and/or change the principle of operation. According to the court in *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification and the Office has not established a *prima facie* case of obviousness. Clearly, if the carbohydrate core, with or without the movable arms, of Brask is introduced into the Nefzi structure, then the required rigidity of the Nefzi structure is lost. Likewise, while Nefzi uses the maleimide function, without linkers, to anchor thiol peptides in a rigid scaffold structure, the removal of the Brask dynamic linkers destroys the dynamic conformation of Brask. It is simply not reasonable of the Office to suggest that one of skill in the art, in contemplating Brask, would have ever reached Applicants' invention, even in light of Nefzi.

Taking this line of discussion further, Applicants question how, exactly, one would combine the two to reach the instant invention. Would one of skill in the art combine the thiopeptide of Nefzi with the aminoxy-functionalized carbohydrate template of Brask, as the Office suggests on page 7 of the September 27, 2007 Office Action? If so, how would one ligate the aminoxy-functionalized carbohydrate template of Brask with the maleimide template of Nefzi? Further, how would one know whether or not to use linkers? How would one know what chemical steps to follow in synthesizing each intermediate required to obtain, from the starting products of Brask and Nefzi, the final product of Applicants' invention? Applicants again emphasize that there is no clear path to follow in combining the elements of Brask and Nefzi in order to come up with the instant invention. Each of Brask and Nefzi has as an objective a particular type of templated synthetic protein, and each sets out a process for obtaining such a protein. With Brask, the desired protein is a **dynamic molecule with moveable arms, providing flexibility in structure.** With Nefzi, the desired protein is **a rigid structure so that the four alpha helix structures are presented in an upright and parallel position,** extending from the template base. These two end products are not compatible. With such uncertainty at every step of the protein synthesis process, it is simply not reasonable for the Office to suggest that it is obvious to combine Brask and Nefzi in order to reach Applicants' claimed invention.

Thus, the fact that isolated elements of an invention are “disclosed” in the prior art is alone insufficient. The test is not whether isolated “elements” are known, but rather whether the subject matter of the invention “as a whole,” in light of all the teachings of all the cited references in all of their entireties, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Still another important point to note in considering whether it would have been obvious to one of skill in the art to combine Brask with Nefzi to come up with Applicants’ claimed invention is the fact that Brask, at the time the cited reference was written, was clearly aware of the work of Mutter, who is the lead author and scientist on the Nefzi reference. Brask, whose 1999 reference cites Mutter’s work (page 290; also see cited references Nos. 5, 6 and 7 on page 299 of Brask), would clearly have been aware of the 1995 Nefzi reference, and yet Brask IN NO WAY suggests or teaches the present invention, or even discusses the Nefzi reference as being relevant to the construction of synthetic proteins on a carbohydrate scaffold. In light of the facts that (1) Brask is clearly “one of skill in the art,” and (2) Brask was aware of Mutter’s work but did not consider the use of any parts of the Nefzi structure as being relevant to the formation of proteins built on a carbohydrate core, it is unreasonable of the Office to suggest that it would have been obvious to a person of skill in the art to combine Brask with Nefzi to come up with Applicants’ invention.

In light of the foregoing discussion and the fact that all of claimed limitations are not disclosed or suggested by the cited combination and/or the proposed combination will render the invention of both references either inoperable or no longer functioning as intended, it is clear that the Office has not met its burden of establishing a *prima facie* case of obviousness. Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

#### Fees Payable

Applicants believe that no fee is due for entry of this amendment, but authorization is hereby given to charge any deficiency in applicable fees for this response to Deposit Account No. 13-4365 of Moore & Van Allen PLLC.

#### Conclusion

Applicants believe this response to the Office Action fully addresses the issues raised by the Examiner Lewis, and places the claims in a form for allowance. If any issues remain outstanding incident to the

allowance of the application, Examiner Lewis is requested to contact the undersigned attorney at (919) 286-8145.

Respectfully submitted,

  
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